ENZYMES "WORK BACKWARDS"

SEEKING SUGAR DADDY

LONDON—When an upstart research company tells pharmaceutical firms it has the technology to propel their carbohydrate-based compounds from research curiosities to clinical-stage therapeutics and diagnostics, the pharmaceutical companies will be skeptical, but they might just listen.

That must be the hope of Glycorex (Lund, Sweden), a company built around the enzymatic-synthesis technology developed by its president, Kurt Nilsson. Glycorex holds a broad U.S. patent on complex-carbohydrate synthesis using glycosidases, enzymes which normally hydrolyze bonds between sugars. By manipulating the concentration and the chemical structure of the carbohydrate substrates, however, Nilsson has persuaded the enzymes to "work backwards," he says, to catalyze synthesis. Several patents on specific applications of the method are pending.

Other companies use enzymes to synthesize complex carbohydrates. However, most of their work—that at Cytel (La Jolla, CA) and Glycomed (Almeda, CA), for instance—is based on glycosyl transferases. Glycosyl transferases are thought of as highly specific enzymes, limited in their substrate range. This, according to Cytel's vice president of glycobiology research, Jim Paulson, provides "a clean reaction. You get a single product." Companies like Cytel and Glycomed use glycosyl transferases to produce the few carbohydrate compounds and their derivatives in which the companies have a strong proprietary position. Enzymes are merely one tool in their research programs.

Technology looks for applications

In contrast, Glycorex has a technology looking for applications. Jim Liebel, Glycorex's U.S.-based vice president of business development, is talking to major pharmaceutical and biotechnology companies to try to identify both applications and corporate partners. He believes that the major need of companies interested in carbohydrates is to uncork the production bottleneck. "If you're locked into organic synthesis for carbohydrates, it's nearly impossible to scale up," says Liebel.

Liebel hopes to seal the first corporate deal within the next few months, or at least before the end of the year. Ambitiously, he expects to persuade collaborators to accept a two-stage package. First there would be up-front sponsorship of research that would lead to Glycorex filing patents on bulk-production methods for specific compounds of interest to clients. In the second stage, Glycorex would license that patented technology on an exclusive basis back to the collaborator. That may be somewhat ambitious, commentators believe, given pharmaceutical companies' sensitivities to divulging information on lead compounds.

Nilsson sees several advantages of glycosidases over glycosyl transferases. "Glycosyl transferases are very expensive to produce," he says. "None are available commercially. And you can't use the enzymes to catalyze a very large range of reactions." On the other hand, glucosidases, as hydrolases, are more abundant. And their catalysis is promiscuous, so they can accommodate a wider range of sugar donors and acceptors and produce a wider range of products. That could be a disadvantage, of course, in that yields of unwanted byproducts might be expected to be higher as well. However, Nilsson is confident that he has systematically tamed the reaction. By modifying the incoming substrate, he can control the anomericity of the product to obtain either alpha-linked or beta-linked compounds. He can also control the linkage position between the sugar residues and the yield of the desired product.

Additional tricks

Cytel's Paulson feels that Glycorex's technology represents a valid approach. "It offers additional tricks that a carbohydrate chemist already familiar with enzymes could use," he says. However, Cytel would only be interested in using the method "if we couldn't get the glycosyl transferases," says Paulson. That seems unlikely, though, as Cytel already has proprietary interests in around a dozen cloned glycosyl transferases, as well as the ability to "fish out" the cDNAs of additional enzymes.

Despite the intense interest in carbohydrate compounds, the area lacks a certain momentum at present. Chembiomed (Edmonton, Alta.)—widely regarded as a good company but one lacking a research focus—folded last year. BioCarb (Lund, Sweden) also folded in 1991 when Swedish banks called in the debts of its billionaire owner, Erik Penser. Ironically, Glycorex is backed, through Liebel, by a consortium of Swedish banks. Although the level of initial funding has not been disclosed, it will only support the growth of the company at about five people a year over the next three years. Yet Liebel expects that "the right corporate partner" will be impressed enough with Glycorex to take an equity stake.

—**John Hodgson**